AR201-13272A

HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For the

Diethylbenzene-Rich Streams Category

Prepared by:

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Ethylbenzene Panel HPV Task Group
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EXECUTIVE SUMMARY

The Ethylbenzene Panel (Panel) of the American Chemistry Council and the Panel's member companies of the Diethylbenzene-Rich Streams HPV Task Group (Task Group) have committed to develop screening level human health, environmental effects and fate, and physicochemical data for the Diethylbenzene-Rich Streams category under the Environmental Protection Agency's (EPA's) High Production (HPV) Challenge Program (Program).

This test plan for the Diethylbenzene-Rich Streams category addresses two streams that contain a predominance of diethylbenzene isomers (87.4 – 98.8 wt%) and are produced during ethylbenzene manufacture. Samples of the streams will be combined to form a test sample for testing.

Chemical Name	Other Name	CAS No.
Diethylbenzene	Mixed Diethylbenzenes	25340-17-4
Benzene, ethylenated, by-products from	Polyethylbenzenes	68608-82-2

Physical/Chemical Properties

Melting point, boiling point, vapor pressure, partition coefficient, and water solubility of Diethylbenzene-Rich Streams will be evaluated as part of the test plan.

Environmental Fate/Pathways

There is adequate information on the biodegradation of Diethylbenzene-Rich Streams. Since there is inadequate information on photodegradation, stability in water, and transport between compartments (fugacity modeling), these studies will be conducted as part of the test plan.

Ecotoxicity

The existing data on the acute toxicity of Diethylbenzene-Rich Streams to fish, aquatic invertebrates, and aquatic plants are adequate to address the endpoints in the HPV Program. Therefore, no ecotoxicity testing of Diethylbenzene-Rich Streams will be conducted.

Human Health Effects

The existing data on the potential human health hazards of Diethylbenzene-Rich Streams are adequate to address the toxicity endpoints in the HPV Program, including acute oral and dermal toxicity, repeated dose toxicity, *in vitro* and *in* vivo genetic toxicity, and developmental toxicity and reproductive toxicity. Therefore, no toxicity testing of Diethylbenzene-Rich Streams will be conducted.

LIST OF MEMBER COMPANIES
ETHYLBENZENE PANEL
DIETHYLBENZENE HPV TASK GROUP

BP Amoco Chemical Company

Chevron Phillips Chemical Company LP

The Dow Chemical Company

Koch Specialty Chemical Company; a Division of Koch Petroleum Company

Sterling Chemicals Inc.

TABLE OF CONTENTS

TEST PLAN FOR THE DIETHYLBENZENE-RICH STREAMS CATEGORY

TEST PLAN FOR THE DIETHYLBENZENE-RICH STREAMS CATEGORY

1. INTRODUCTION

The Ethylbenzene Panel (Panel) of the American Chemistry Council and the Panel's member companies of the Diethylbenzene-Rich Streams HPV Task Group (Task Group) have committed to develop screening level human health, environmental effects and fate, and physicochemical data for the Diethylbenzene-Rich Streams category under the Environmental Protection Agency's (EPA's) High Production (HPV) Challenge Program (Program).

In preparing this test plan, the Task Group has given careful consideration to the principles contained in the letter EPA sent to all HPV Challenge Program participants on October 14, 1999. As directed by EPA in that letter, the Panel has sought to maximize the use of scientifically appropriate categories of related chemicals and structure activity relationships. Additionally, and also as directed in EPA's letter, the Task Group has conducted a thoughtful, qualitative analysis of the adequacy of existing data. The Task Group has taken the same thoughtful approach when developing its test plan. The Task Group believes its test plan conforms to the principles articulated in EPA's letter.

This plan identifies two CAS numbers used to describe the streams in the category, identifies data of adequate quality for substances included in the category and individual isomers of Diethylbenzene and outlines testing needed to develop screening level data for this category under the Program. This document also provides the testing rationale for the Diethylbenzene-Rich Streams category. The objective of this effort is to identify and develop sufficient test data and/or other information to adequately characterize the human and environmental fate for the category in accordance with the EPA HPV Program.

II. DESCRIPTION OF THE DIETHYLBENZENE-RICH STREAMS CATEGORY

The proposed category is defined as Diethylbenzene-Rich Streams. This category consists of streams that contain a predominance of diethylbenzene isomers and are produced during ethylbenzene manufacture.

Ethylbenzene is produced through alkylation of benzene with ethylene. In addition to the production of ethylbenzene, there are side reactions that involve the reaction of ethylene with ethylbenzene to produce diethylbenzene, and, to a much lesser extent, further

alkylations to produce triethylbenzene and polyethylbenzene. In addition, butylbenzene and other alkylaromatics may be formed in varying limited amounts. After the ethylbenzene is removed, the remaining stream is separated into a diethylbenzene-rich stream and a bottoms stream. Some manufacturers may further process the diethylbenzene-rich streams to increase the diethylbenzene content. The diethylbenzene-rich streams are identified by two CAS Registry Numbers:

Chemical Name	Other Name	CAS No.
Diethylbenzene	Mixed Diethylbenzenes	25340-17-4
Benzene, ethylenated, by-products from	Polyethylbenzenes	68608-82-2

The composition of both diethylbenzene-rich streams is listed below based on capillary GC analysis of samples submitted by the four participating companies to BP Amoco Analytical Technology (BP Amoco, 2000).

Component	Wt %
Diethylbenzenes'	87.6 98.8
Triethylbenzenes	<5.1
Polyethylbenzenes	<0.1
Iso-/sec-butylbenzenes	0.6 - 1.1
Other alkylbenzenes	0.7 - 4.5
Ethylbenzene	<1.9
Benzene	<0.1
Diphenylalkanes	<0.1
Ethyl diphenylethanes and Diethyl biphenyls	<0.1
PNAs (3-rings)	<0.1
Paraffins/Naphthenes	<1.6
Total of unidentified components, each present at <0. 1%	<1.4

'n-butylbenzene coeluted with 1,4-diethylbenzene

As shown in the table above, the range of composition for both Diethylbenzene-Rich Streams (CAS No. 25340-l 7-4 and CAS No. 68608-82-2) are very similar. For purposes of the proposed testing, equal quantities of the streams from each of the four sponsoring companies will be combined to form a representative test sample of Diethylbenzene-Rich Streams.

III. SUMMARY OF EXISTING INFORMATION AND TEST PLAN RATIONALE

Existing information on Diethylbenzene-Rich Streams and diethylbenzene isomers is summarized below. The SIDS endpoints with sufficient data for the HPV program are summarized in Appendix 1.

A. Physical/Chemical Properties

Melting point, boiling point, vapor pressure, partition coefficient, and water solubility of Diethylbenzene-Rich Streams will be evaluated as part of the test plan.

There are reported data for these endpoints for diethylbenzene isomers but not for Diethylbenzene-Rich Streams (HSDB, 2001).

	1,2-Diethylbenzene	1,3-Diethylbenzene	1,4-Diethylbenzene
Boiling Point (“C)	184	181.1	183.7
Melting Point (“C)	-31.2	-83.9	-42.83
Vapor Pressure (mm Hg at 25 “C)	1.05	1.20	1.03
Water Solubility (mg/l at 25 “C)	71.1	24.0	24.8
Octanol/Water Partition Coeff. (log Kow)	3.72	4.44	4.45

B. Environmental Fate/Pathways

There is adequate information on the biodegradation of Diethylbenzene-Rich Streams. Since there is inadequate information on photodegradation, stability in water, and transport between compartments (fugacity modeling), these studies will be conducted as part of the test plan.

1. Biodegradation

In a CO2 evolution test using unacclimated microbial cultures, Mixed Diethylbenzenes degraded 4.7% after 28 days and 5.5% after 35 days, indicating that it is not readily biodegradable (Marks et al., 1995). Similar results were obtained for 1,4-diethylbenzene (MITI, 1993; SIDS Dossier, 1994; SIDS SIAR, 1994). However, acclimated microorganisms completely degraded all three isomers of diethylbenzene at low concentrations ($\leq$ 0.5 mg/l in about 5 days (MHW, 1993c; SIDS Dossier, 1994; SIDS SIAR, 1994; HSDB, 2001).

2. Photodegradation

All three isomers have been reported to photodegrade (HSDB, 2001).

3. Bioaccumulation

A bioaccumulation study in carp demonstrated a moderate potential of 1,4-diethylbenzene to bioconcentrate based on bioconcentration factors (BCF) of 320-629 (MITI,1992; SIDS Dossier, 1994; SIDS SIAR, 1994).

C. Ecotoxicity

The existing data on the ecotoxicity of Diethylbenzene-Rich Streams are adequate to address the endpoints in the HPV Program. Therefore, no ecotoxicity testing of Diethylbenzene-Rich Streams will be conducted.

Mixed Diethylbenzenes was slightly toxic to fish, daphnids, and algae. The LC50 value was 23 mg/l for rainbow trout (Ward et al, 1996a). EC50 values of 39 mg/l (Ward et al., 1996b) and 9.42 mg/l (Tucker et al., 1987a) were reported for *Daphnia magna.* The 96 hour EC50 for the algae *Selenastrum capricornutum* was reported as 47 mg/l (Ward et al, 1996c) and greater than 20.06 mg/l (Tucker et al., 1987b).

1,4-Diethylbenzene was moderately toxic to fish and daphnids, and slightly toxic to algae (EA, 1992; SIDS Dossier, 1994; SIDS SIAR, 1994). The 96-hour LC50 for red killitish was 1.8 mg/l, the 24 hour EC50 for *Daphnia magna* was 32.0 mg/l, and the 72 hour EC50 in the algae *Selenastrum capricornutum* was 29 mg/l. In a daphnid 21-day reproduction study, 1,4-diethylbenzene did not show a tendency for cumulative chronic toxicity: the 48-hour LC50 was 6.0 mg/l: at 21 days, the LC50 was 2.4 mg/l, the reproduction EC50 was 1.3 mg/l, the reproduction LOEC was 3.0 mg/l and the reproduction NOEC was 0.93 mg/l.

D. Human Health Effects

The existing data on the potential human health hazards of Diethylbenzene-Rich Streams are adequate to address the toxicity endpoints in the HPV Program. Therefore, no toxicity testing of Diethylbenzene-Rich Streams will be conducted.

1. Acute Toxicity

Diethylbenzene-Rich Streams are characterized by low acute oral and dermal toxicity. Oral LD_{50} of 2050 to 6900 mg/kg have been reported for Mixed Diethylbenzenes (Chevron, 1991a; Biodynamics, 1987a). In two studies with Mixed Diethylbenzenes, the dermal LD_{50} was reported to be greater than 2000 mg/kg in rats (Chevron, 1991 b) and greater than 5000 mg/kg in rabbits (Biodynamics, 1987b).

The oral LD50 for 1,4-diethylbenzene was greater than 2000 mg/kg in Sprague-Dawley rats (MHW, 1993a; SIDS Dossier, 1994; SIDS SIAR, 1994).

Mixed Diethylbenzenes caused reversible moderate skin irritation (average scores at 24, 48, and 72 hours were 3.1 for erythema and 0.4 for edema; Draize score of 3.4 of a possible 8.0 after a 4-hour exposure) (Chevron, 1990a) and slight to moderate conjunctival irritation (Draize score of 2.7 of a possible 110) (Chevron, 1990b). Mixed Diethylbenzenes tested by Monsanto (1992) caused similar eye and skin irritation. Mixed Diethylbenzenes were negative for skin sensitization potential (Chevron, 1991c).

2. Subchronic Toxicity

Rats were exposed by inhalation to Mixed Diethylbenzenes at 0, 190, 610 and **1400** mg/m^3 for 10 weeks, six hr/day, five days per week (Kaempfe and Thake, 1993). The NOAEL was 190 mg/m^3. Mean body weights were observed in the high-dose group throughout the study. There were no treatment-related abnormal clinical observations or ocular abnormalities. Treatment-related changes in hematologic parameters included moderate decreases in total white cell and lymphocyte counts in the mid- and high-exposure level males. Abnormal sera color (blue or blue-gray) was observed in high-exposure level males and females. Treatment-related changes in serum chemistry parameters included decreases in alanine aminotransferase, aspartate aminotransferase and creatinine phosphokinase in high-exposure level females and increases in potassium in high-level males and phosphorus in males from the high-exposure group and females from the mid- and high-exposure groups. An abnormal blue-gray color was observed in most tissues from all but one high-exposure animal. At the mid-exposure level, the same color was observed in brains and in the urinary bladders of some animals. This abnormal color probably resulted from the presence of the parent chemical or a metabolite in these tissues. There were no other gross or macroscopic changes attributed to the test material, including no effects on reproductive organs of either sex.

Rats were exposed orally to 1,4-diethylbenzene at 0, 30, 150 or 750 mg/kg/day for 28 days in the combined repeat dose and reproductive/developmental toxicity screening test (MHW, 1993a; SIDS Dossier, 1994; SIDS SIAR, 1994). Effects were noted in the livers (increased weights, brown color, and swollen cells) and kidneys (increased weights), with corresponding effects noted in the blood chemistries; however, there were no corresponding histopathologic findings. The no effect level (NOEL) was determined to be 30 mg/kg/day.

3. Neurotoxicity

Subchronic oral studies of Mixed Diethylbenzenes and diethylbenzene isomers which focused on neurotoxicity have been conducted (Gagnaire et al., 1990). Mixed Diethylbenzenes were administered at 0, 500 or 7.50 mg/kg/day for 10 weeks, 5 days/week. In both treated groups, rats exhibited a blue discoloration of the skin and urine and two animals in each group died during the study. A significant reduction in body weight gain was observed from the first week in the high-dose group. Rats in the treated groups developed severe weakness in hind limbs and disturbances in gait that resulted in a complete paralysis of the hind limbs for some rats. There was a time-dependent decrease in motor conduction velocity, sensory conduction velocity and amplitude of the sensory action potential. The LOAEL was 500 mg/kg.

In the studies of the isomers, 1,2-diethylbenzene was administered at 100 mg/kg/day, 4 days/week for 8 weeks, whereas 1,3-diethylbenzene and 1,4-diethylbenzene were each administered at 500 mg/kg/day to rats for five days/week for 8 weeks (Gagnaire et al., 1990). There was an eight-week post-exposure observation period for the isomer studies. Rats given 1,2-diethylbenzene developed the same symptoms (decreased body weight,

blue discoloration of the skin and urine, weakness of hind limbs, paralysis) as those described for the diethylbenzene mixture. Two rats died during the study. 1,3-Diethylbenzene and 1,4-diethylbenzene-treated rats did not display any signs of neurotoxicity or any other signs of systemic toxicity. During the recovery period, the 1,2-diethylbenzene treated rats regained weight and became more mobile, but presented trailing hind limbs when attempting to walk. On the 4^{th} week of recovery, all animals treated with 1,2-diethylbenzene succeeded in standing up. A time-dependent decrease in motor conduction velocity, sensory conduction velocity and amplitude of the sensory action potential was observed in animals dosed with 1,2-diethylbenzene but not with 1,3- or 1,4-diethylbenzene. The LOAEL for 1,2-diethylbenzene was 100 mg/kg whereas the NOAEL was 500 mg/kg for 1,3- and 1,4-diethylbenzene.

In additional neurotoxicity evaluations, rats were exposed to a commercial mixture of diethylbenzene isomers by inhalation at approximately 500, 600, 700, 800 or 900 ppm for 6 hrs/day, 5 days/week, for 18 weeks (Gagnaire et al., 1992a). There were treatment-related weakness or paralysis of the hindlimbs and disturbance of gait (not observed at 500 ppm), changes in motor and sensory nerve conduction velocities, changes in amplitude of the sensory action potential, and/or changes in parameters of the brainstem auditory evoked potential. Thus, in these studies, diethylbenzene was neurotoxic following repeated exposure to high levels. Rats exhibited a blue discoloration of tissues and urine. A NOEL was not determined, but the lack of clinical signs at 500 ppm indicates a decreased response at that exposure level.

When administered by ip injection 4 days/week at 10 mg/kg for 11 weeks or at 2 mg/kg for 6 weeks, the metabolite 1,2-diacetylbenzene caused hindlimb weakness at 10 mg/kg, hindlimb weakness and disturbance in gait at 20 mg/kg, and a decrease in mean sensory and motor conduction velocities at both dose levels (Gagnaire et al., 1991).

In another study, 1,2-diethylbenzene administered orally at 75 and 100 mg/kg/day, 4 days/week for 8 weeks, and intraperitoneal injection of 1,2-diacetylbenzene at 10 or 15 mg/kg/day, 4 days/week for 8 weeks, produced time- and dose-dependent alteration in brainstem auditory evoked potentials which did not completely recover during an 8 or 10 week recovery period (Gagnaire et al., 1992b).

4. Genetic Toxicity

Mixed Diethylbenzenes was negative for the reverse mutation assay with Salmonella *typhimurium* strains TA98, TA100, TA1535, and TA 1537 with and without S-9 activation (Chevron, 1991d; Stankowski, 1988), and with *E. coli* WP2 uvrA with and without S-9 activation (Chevron, 1991d). Mixed Diethylbenzenes was also negative in an *in vivo* micronucleus study in which mice were dosed intraperitoneally with 1000, 2000, or 4000 mg/kg (Chevron, 1991 e). In a chromosomal aberration study using Chinese hamster ovary cells, Mixed Diethylbenzenes was negative with and without S-9 activation (Myers and Fahey, 1989).

1,4-Diethylbenzene was also negative in a bacterial reverse mutation assay (Salmonella *typhimurium* TA98, TA100, TA1535, TA1537, TAI 538, and *E. coli* uvrA with and without metabolic activation) (MHW, 1993b; SIDS Dossier, 1994; SIDS SIAR, 1994). It was also negative in a Chinese hamster CHL cytogenetics assay with and without metabolic activation (MHW, 1993b; SIDS Dossier, 1994; SIDS SIAR, 1994).

5. Developmental Toxicity

Mixed Diethylbenzenes administered orally to pregnant rats on gestation days 6-16 at 20, 100 and 200 mg/kg did not cause birth defects or developmental variations (Mercieca, 1992). The NOEL for maternal toxicity (reduced body weights and food consumption) was 20 mg/kg, whereas the NOEL for fetal body weight effects was 100 mg/kg. Mixed Diethylbenzenes streams was not teratogenic in this study.

1,2-Diethylbenzene was administered orally to pregnant Sprague-Dawley rats at 0 (corn oil vehicle), 5, 15, 25 and 35 mg/kg on gestation days 5-20 (Saillenfait et al., 1999). Maternal weight gain and food consumption were decreased in the rats that received 15, 25 and 35 mg/kg. There was no effect on number of live fetuses, implantations, non-surviving implantations per litter, or fetal sex ratios. Fetal body weights were reduced in a dose-related fashion in the groups receiving 15, 25 and 35 mg/kg. The NOEL for both maternal and fetal toxicity was 5 mg/kg. There was no treatment-related effect on external visceral and skeletal malformations. 1,2-Diethylbenzene was not teratogenic in this study.

6. Reproductive Toxicity

In the subchronic inhalation study reported by Kaempfe and Thake, 1993 (see above), rats exposed by inhalation to Diethylbenzene-Rich Streams at 0, 190, 610 and 1400 mg/m^3 for 10 weeks, six hr/day, five days per week had no effects on reproductive organs of either sex.

Sprague-Dawley rats were dosed orally with 1,4-diethylbenzene at 0, 30, 150 or 750 mg/kg/day in the combined repeat dose and reproductive/developmental toxicity screen level (MHW, 1993a; SIDS Dossier, 1994; SIDS SIAR, 1994). Males were dosed for 44 days, including 14 days before mating and females from 14 days before mating until Day 3 of lactation. There were no effects on mating, fertility, estrus cycle, pup body weight, or gross abnormalities at any dose. A slight increased in duration of gestation and a slight decrease in viability index at Day 4 in male pups in the 750 mg/kg/day group were not considered treatment-related by the investigators.

Based on the lack of effects on reproductive organs in the subchronic inhalation study (Kaempfe and Thake, 1993) and the availability of the developmental study (Mercieca, 1992) as well as the reproduction screen with 1,4-diethylbenzene, there is sufficient information on reproduction endpoints for the HPV progam.

7. Toxicokinetics

In pregnant Sprague-Dawley rats given a single oral dose of 25 mg/kg, [^{14}C] 1,2-diethylbenzene concentrations in the fetus measured at 28-60% of the levels in maternal plasma within the first 48 hours after dosing and were consistently lower than levels in the placenta (Saillenfait et al., 1999). Placental and fetal tissues accounted for < 0.35% of the administered dose. Thus, there was limited placental transfer to the developing rat Fetus.

Gagnaire et al. (1991) reported 1,2-diacetylbenzene in urine from rats given 165 mg/kg 1,2-diethylbenzene orally on four consecutive days. In male Sprague-Dawley rats administered [^{14}C] 1,2-diethylbenzene intravenously (1 mg/kg) or oral (1 or 100 mg/kg), radioactivity was rapidly absorbed and mainly excreted in the urine (6576% of the dose), and to a lower extent in the feces (15-23% of the dose) or via exhaled air (3-5% of the dose) (Payan et al., 1999). Biliary metabolites were extensively reabsorbed from the gut and ultimately excreted in urine. The two main metabolites were two glucuronide conjugates, probably of the two enantiomers of 1 -(2'-ethylphenyl) ethanol, suggesting that the main initial conversion step of the primary metabolic pathway appears to be the hydroxylation of the a-carbon of the side chain. In this study, insignificant amounts of the neurotoxic metabolite 1,2-diacetylbenzene were detected in urine, bile and feces. Payan et al. (2001) reported that the two main metabolites of 1,2-diethylbenzenes in urine of treated rats are the glucuronide conjugates of two enantiomers of 1-(2'-ethylphenyl)ethanol. The metabolic steps which lead to the conjugates are under stereoselective control.

8. Carcinogenicity

A study of the dermal carcinogenesis potential of diethylbenzene (composition not given) (10% in acetone) applied to the backs of C3H/HEJ mice found one squamous cell carcinoma whereas none were reported in control mice (BRRC, 1983). Historical control data were not presented.

IV. TEST PLAN SUMMARY

HPV Category: Diethylbenzene Streams
(CAS No. 25340-l 7-4 and CAS No. 68608-82-2)

Adequate information is available to address the following HPV endpoints:

	Adequate Data Available
3.5	Biodegradation
4.1	Acute Toxicity to Fish
4.2	Acute Toxicity to Aquatic Invertebrates
4.3	Toxicity to Aquatic Plants (e.g. Algae)
5.1.1	Acute Oral Toxicity
5.1.3	Acute Dermal Toxicity
5.4	Repeated Dose Toxicity
5.5	Genetic Toxicity *In Vitro*
5.6	Genetic Toxicity *In Vivo*
5.9	Developmental Toxicity/Teratogenicity
5.8	Reproductive Toxicity

The study plan for Diethylbenzene-Rich Streams will address the following HPV endpoints:

	Inadequate Data and/or Datagaps
2.1	Melting Point
2.2	Boiling Point
2.4	Vapor Pressure
2.5	Partition Coefficient
2.6	Water Solubility
3.1.1	Photodegradation
3.1.2	Stability in Water
3.3.1	Fugacity Model I or III

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Appendix 1: Summary of HPV Endpoints with Existing Sufficient lnformation for Diethylbenzene-Rich Streams

HPV SIDS Endpoints	Test Material*	Data Summary	Reference
3.5 Biodegradation	1	Not readily biodegradable. 4.7% after 28 days; 5.5% after 35 days	Marks et al., 1995
4.1 Acute Toxicity to Fish	1	96-hour LC_{50} = 23 mg/liter NOEC (96 hour) = 13 mg/liter	Ward et al., 1996a
4.2 Acute Toxicity to Aquatic Invertebrates	1	(A) EC_{50} = 39 mg/liter NOEC (48 hour) < 13 mg/liter (B) EC_{50} = 9.42 mg/liter	(A) Ward et al., 1996b (B) Tucker et al., 1997
4.3 Toxicity to Aquatic Plants (e.g., Algae)	1	(A) Growth rate (72 and 96 hr): EC_{50} = 63 and 66 mg/l; NOEC = 25 mg/l Cell density (72 and 96 hr): EC_{50} = 41 and 47 mg/l; NOEC = 13 and 25 mg/l (C) Biomass effects (96 hr): EC_{50} = >20.06 mg/l	(A) Ward et al., 1996c (B) Tucker et al., 1997
5.1.1 Acute Oral Toxicity	1	(A) Rat LD_{50} = 2050 mg/kg (both sexes) (B) Rat LD_{50} = 6900 mg/kg (males) and 4700 mg/kg (females)	(A) Biodynamics, 1987 (B) Chevron, 1991a
5.1.3 Acute Dermal Toxicity	1	(A) Rabbit LD_{50} = >5000 mg/kg (B) Rat LD_{50} = >2000 mg/kg	(A) Biodynamics, 1987 (B) Chevron, 1991b
5.4 Repeated Dose Toxicity	1,2,3	(A) NOAEL = 190 mg/m^3 (B,C) Specialized neurotoxicity studies: Oral: LOAEL = 500 mg/kg/day Inhalation: LOAEL = 500 ppm	(A) Kaempfe and Thake, 1993 (B) Gagnaire et al., 1990 (C) Gagnaire et al., 1992a
5.5 Genetic Toxicity *In Vitro*	1	(A, B) Negative for bacterial mutations (C) Negative for chromosomal aberration in Chinese hamster ovary cells	(A) Chevron et al., 1991a (B) Stankowski, 1988 (C) Myers and Fahey, 1989
5.6 Genetic Toxicity *In Vivo*	1	Negative for micronuclei in bone marrow erythrocytes	Chevron, 199 1 e

Appendix 1 (continued): Summary of HPV Endpoints with Existing Sufficient Information for Diethylbenzene-Rich Streams

HPV SIDS Endpoints	Test Material*	Data Summary	Reference
5.8 Reproductive Toxicity	1,3	(A) No effect on reproductive organs in subchronic study (B) Reproduction screen with 1,4-diethylbenzene. NOAEL = 750 mg/kg/day	(A) Kaempfe and Thake, 1993 (B) MHW, 1993a; SIDS Dossier, 1994; SIDS SIAR, 1994
5.9 Developmental Toxicity	1,3	(A) Rat oral gavage with Mixed Diethylbenzenes Maternal NOAEL = 20 mg/kg/day Developmental NOAEL = 100 mg/kg/day (B) Rat oral gavage with 1,2-DEB Maternal NOAEL = 5 mg/kg/day Developmental NOAEL = 5 mglkglday	(A) Mercieca, 1992 (B) Saillenfait et al., 1999

*Test Material code:

1 = Mixed Diethylbenzene Stream (CAS No. 25340- 17-4)
2 = Diethylbenzene isomers (mixed)
3 = 1,2- or 1,3- or 1,4-diethylbenzene